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A Non-rewarding, Non-aversive Buprenorphine/Naltrexone Combination Attenuates Drug-primed Reinstatement to Cocaine and Morphine in Rats in a Conditioned Place Preference Paradigm

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Concurrent use of cocaine and heroin is a major public health issue, with no effective relapse prevention treatment available. Buprenorphine is a partial agonist at the mu-opioid receptor, as well as a kappa-opioid receptor antagonist. Naltrexone is a mu- and kappa-opioid receptor antagonist. There is interest in a buprenorphine/naltrexone combination (Rothman et al., 2000) as an anti-relapse therapy, which would act as a functional kappa-opioid receptor antagonist and mu-opioid receptor antagonist/partial agonist. We investigated the ability of a buprenorphine/naltrexone combination to inhibit reinstatement to morphine- and cocaine-seeking in male Sprague Dawley rats (250-420g). All drug injections were i.p.

Treatments for relapse prevention should not themselves be abusable. As buprenorphine alone is rewarding via activation of the mu-opioid receptor, we determined the dose of naltrexone required to block this effect. Rats were trained to exhibit buprenorphine-induced conditioned place preference: 4 x 40-minute drug conditioning sessions and 4 x 40-minute saline conditioning sessions over 8 days, followed by a 15-minute free-to-explore test session; CPP score calculated such that if a rat spent equal time in the drug-paired and the saline-paired compartments on test-day, CPP = 0%. Buprenorphine alone (0.3 mg/kg) induced significant CPP (10.4 ± 3.7%, n = 15, $p < 0.05$, 1-tailed Wilcoxon matched pairs signed-rank test compared to baseline) whereas when naltrexone was co-administered with buprenorphine there was a dose-dependent decrease in buprenorphine-induced CPP; rats trained with 0.3 mg/kg buprenorphine + 1.0 mg/kg naltrexone showed no difference from baseline, CPP: -1.5 ± 6.6%, n = 8, $p > 0.05$. Interestingly, 3.0 mg/kg naltrexone (co-administered with 0.3 mg/kg buprenorphine) not only blocked the rewarding effects of buprenorphine, but caused conditioned place aversion (CPP: -10.6 ± 4.6 %, n = 16, $p < 0.05$).

Having demonstrated that a combination of 0.3 mg/kg buprenorphine and 1.0 mg/kg naltrexone was neither rewarding nor aversive, we tested its ability to inhibit drug-primed reinstatement. Rats were conditioned using 3 mg/kg cocaine or 5 mg/kg morphine (1x drug- and 1x saline- conditioning session per day for 3 days (20-minute sessions for cocaine, 40-minute sessions for morphine). Extinction was achieved by daily saline injection followed by confinement to each compartment for 20 minutes a day. Drug-primed reinstatement was elicited by 3 mg/kg cocaine or 1.25 mg/kg morphine immediately followed by a 30-minute free-to-explore test. Reinstatement data was analysed using Friedman test with Dunn's multiple-comparison test. Both cocaine- and morphine-priming elicited clear reinstatement of CPP (cocaine: 11.4 ± 5.2%, n = 12, $p < 0.05$; morphine: 16.3 ± 6.1%, n = 14, $p < 0.05$). However, a single buprenorphine/naltrexone injection (0.3 / 1.0 mg/kg), administered 10 minutes prior to drug priming, inhibited both cocaine-primed reinstatement in cocaine-conditioned rats (CPP = -9.5 ± 6.0%, n = 9, $p > 0.05$) and morphine-primed reinstatement in morphine-conditioned rats (CPP = 5.8 ± 10.2 %, n = 8, $p > 0.05$).

These data add to the growing evidence that a buprenorphine/naltrexone combination may be protective against relapse in a polydrug abuse situation.

Rothman RB et al. (2000) *J. Subst. Abuse Treat.*, **18**, 277-81.